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PATENT SPECIFICATION

(11) 1 206 216

1 206 216

NO DRAWINGS

- (21) Application No. 23194/68 (22) Filed 15 May 1968
 (31) Convention Application No. 654 069 (32) Filed 18 July 1967 in
 (33) United States of America (US)
 (45) Complete Specification published 23 Sept. 1970
 (51) International Classification C 07 d 9/00
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 C2C 1K2A1 1K2C3 1K2D 1Q5 1Q6B1 1Q6C 1Q7B 1Q8A
 1Q9B 1Q9C 1Q9D2 1Q9F1 1Q9F2 1Q9K 1Q9L



(54) AMINOPROPYLIDENE DIBENZOXEPINE TRANQUILIZERS

PATENTS ACT 1949

SPECIFICATION NO. 1,206,216

The following corrections were allowed under Section 76 on 6 May 1970.

Page 1, line 1, after 'We,' insert 'PFIZER Inc., formerly known as'

THE PATENT OFFICE
7 June 1971

R 3376/28

15 certain novel 2 - substituted - 11 - amino-
propylidene - 6,11 - dihydrodibenz[b,e]-
oxepines and their acid additions salts, which
have been found to be useful in therapy as
tranquilizing agents.

20 In the past, very few workers have ever
attempted to prepare tricyclic heterocycles con-
taining a trifluoromethylthio or trifluoro-
methylsulfonyl grouping on the aromatic ring
principally due to the difficulty involved in
the chemical technology required. The only
25 known literature available on this subject is
that of E.A. Nodiff et al. appearing in the
Journal of Organic Chemistry, Vol. 25, page
60 (1960) and M. Gordon et al. in *Arzneimit-
tel Forschung*, Vol. 4, page 318 (1962), where
30 the 2 - trifluoromethylsulfonyl and 2 - tri-
fluoromethylthio analogs of chlorpromazine
were both prepared and found to have im-
proved pharmacological properties as com-
pared to chlorpromazine itself. Unfortunately,
35 these latter correlations were of limited value
outside the phenothiazine field. For instance,
such valuable phenothiazine group substituents
as trifluoromethyl and dimethylsulfonamido
40 were both found to be of little value in the
field of dibenzoxepines where they did not lead
to compounds possessing potent biological in-
terest.

45 In accordance with the present invention,
there is now provided for the first time a novel
class of aminopropylidene base compounds
which are tricyclic in nature and which do

CH₂O

and the pharmaceutically-acceptable acid addi- 55
tion salts thereof, wherein Y is sulfur, sulfinyl
or sulfonyl; and Z is lower alkylamino, di-
(lower alkyl)amino, pyrrolidino, piperidino,
homopiperidino, morpholino, thiamorpholino,
piperazino, N - (lower alkyl)piperazino or N- 60
(lower hydroxyalkyl)piperazino, wherein said
lower alkyl moieties each contain up to four
carbon atoms. These compounds are all potent
CNS depressants and hence, of value as tran- 65
quilizing agents for use in the treatment of
mental anxiety and nervous tension.

Among the typical member compounds of
this series which are included within the pur-
view of the present invention are such dibenz-
oxepine derivatives as 2 - trifluoromethyl- 70
sulfonyl - 11 - (3 - N,N - dimethylamino-
propylidene) - 6,11 - dihydrodibenz[b,e]ox-
epine, 2 - trifluoromethylthio - 11 - (3 - N-
monomethylaminopropylidene) - 6,11 - di-
hydrodibenz[b,e]oxepine, 2 - trifluoromethyl- 75
sulfonyl - 11 - (3 - N - monomethylamino-
propylidene) - 6,11 - dihydrodibenz[b,e]ox-
epine, 2 - trifluoromethylsulfonyl - 11 - (3-
N - piperazinopropylidene) - 6,11 - dihydro-
dibenz[b,e]oxepine, 2 - trifluoromethyl- 80
sulfonyl - 11 - [3 - (4 - methyl - 1 - piper-
azinyloxy)propylidene] - 6,11 - dihydrodibenz-
[b,e]oxepine and 2 - trifluoromethylsulfonyl-
11 - [3 - (4 - β - hydroxyethyl - 1 - piper-

[Price 5s. 0d. (25p)]

SEE CORRECTION SLIP ATTACH

Amg

PATENT SPECIFICATION

(11) 1206216

NO DRAWINGS

- (21) Application No. 23194/68 (22) Filed 15 May 1968
 (31) Convention Application No. 654 069 (32) Filed 18 July 1967 in
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 C2C 1K2A1 1K2C3 1K2D 1Q5 1Q6B1 1Q6C 1Q7B 1Q8A
 1Q9B 1Q9C 1Q9D2 1Q9F1 1Q9F2 1Q9K 1Q9L



(54) AMINOPROPYLIDENE DIBENZOXEPINE TRANQUILIZERS

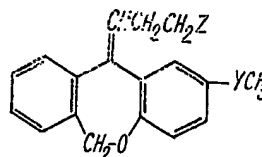
(71) We, CHAS. PFIZER & CO., INC., a Corporation organized under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York 17, State of New York, United States of America, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to various new and useful aminopropylidene dibenzoxepine compounds. More particularly, it is concerned with certain novel 2 - substituted - 11 - aminopropylidene - 6,11 - dihydrodibenz[b,e]-oxepines and their acid additions salts, which have been found to be useful in therapy as tranquilizing agents.

In the past, very few workers have ever attempted to prepare tricyclic heterocycles containing a trifluoromethylthio or trifluoromethylsulfonyl grouping on the aromatic ring principally due to the difficulty involved in the chemical technology required. The only known literature available on this subject is that of E.A. Nodiff et al. appearing in the *Journal of Organic Chemistry*, Vol. 25, page 60 (1960) and M. Gordon et al. in *Arzneimittel Forschung*, Vol. 4, page 318 (1962), where the 2 - trifluoromethylsulfonyl and 2 - trifluoromethylthio analogs of chlorpromazine were both prepared and found to have improved pharmacological properties as compared to chlorpromazine itself. Unfortunately, these latter correlations were of limited value outside the phenothiazine field. For instance, such valuable phenothiazine group substituents as trifluoromethyl and dimethylsulfonamido were both found to be of little value in the field of dibenzoxepines where they did not lead to compounds possessing potent biological interest.

In accordance with the present invention, there is now provided for the first time a novel class of aminopropylidene base compounds which are tricyclic in nature and which do

possess the aforementioned ring-substituent group requirements on the aromatic ring with subsequently favorable results as to their therapeutic effects. More specifically, these compounds are all members selected from the group consisting of aminopropylidene bases of the formula:



and the pharmaceutically-acceptable acid addition salts thereof, wherein Y is sulfur, sulfinyl or sulfonyl; and Z is lower alkylamino, di-(lower alkyl)amino, pyrrolidino, piperidino, homopiperidino, morpholino, thiomorpholino, piperazino, N - (lower alkyl)piperazino or N-(lower hydroxyalkyl)piperazino, wherein said lower alkyl moieties each contain up to four carbon atoms. These compounds are all potent CNS depressants and hence, of value as tranquilizing agents for use in the treatment of mental anxiety and nervous tension.

Among the typical member compounds of this series which are included within the purview of the present invention are such dibenzoxepine derivatives as 2 - trifluoromethylsulfonyl - 11 - (3 - N,N - dimethylaminopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine, 2 - trifluoromethylthio - 11 - (3 - N-monomethylaminopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine, 2 - trifluoromethylsulfonyl - 11 - (3 - N - monomethylaminopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine, 2 - trifluoromethylsulfonyl - 11 - (3 - N - piperazinopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine, 2 - trifluoromethylsulfonyl - 11 - [3 - (4 - methyl - 1 - piperazinyl)propylidene] - 6,11 - dihydrodibenz[b,e]oxepine and 2 - trifluoromethylsulfonyl - 11 - [3 - (4 - β - hydroxyethyl - 1 - piper-

[Price 5s. 0d. (25p)]

SEE CORRECTION SLIP ATTACHE

aziny]propylidene] - 6,11 - dihydrodibenz-
[b,e]oxepine, including both their *cis* and
trans-isomers, as well as their non-toxic phar-
maceutically-acceptable acid addition salts,
such as the hydrohalides and the like. Of
especial interest in this connection are the *cis*-
isomers of these compounds in view of their
significantly high degree of pharmacological
activity. This is especially true in the case of
the *cis*-isomers of 2 - trifluoromethylsulfonyl-
11 - (3 - N,N - dimethylaminopropylidene)-
6,11 - dihydrodibenz[b,e]oxepine hydro-
chloride and 2 - trifluoromethylthio - 11 - (3 -
N - monomethylaminopropylidene) - 6,11 - di-
hydrodibenz[b,e]oxepine hydrochloride, which
have both been found to be highly potent CNS
depressants with a long duration of action.

The process employed for preparing the
novel compounds of this invention involves
treating the appropriate 2 - CF₃Y - substitu-
ted - 6,11 - dihydrodibenz[b,e] - oxepine-
11 - one with a phosphorane compound of the
formula (R)₃P=CHCH₂CH₂Z, where R is
alkyl containing up to six carbon atoms,
phenyl, aminophenyl or benzyl, and Z is as
hereinbefore defined. This particular reaction
step is normally carried out in a reaction-inert
polar organic solvent medium, preferably em-
ploying a slight excess of the phosphorane
compound, e.g., about a 20% molar excess,
at a temperature ranging from between about
15°C. and about 100°C. for a period of about
one-half to about twenty hours. Preferred
reaction-inert polar organic solvents for use in
this connection include such open chain or
cyclic ethers as diethyl ether, di-isopropyl
ether, tetrahydrofuran and dioxane, as well as
such polar organic solvents as the N,N - di-
(lower alkyl)alkanoamides like dimethylform-
amide, diethylformamide and dimethylacet-
amide, and the lower dialkyl sulfoxides and
sulfones such as dimethyl sulfoxide, diethyl
sulfoxide and di - n - propyl sulfone. Upon
completion of this Wittig-type reaction, the
desired aminopropylidene base compound is
either isolated from the reaction mixture as
such or else converted to an acid addition salt
thereof and the latter compound is then sub-
sequently recovered from the mixture by means
well-known to those skilled in the art. The
acid addition salt can then be further purified
and used as such, if it is pharmaceutically-
acceptable, or it may be converted back to the
free organic base compound or to another
pharmaceutically-acceptable acid addition salt,
if so desired.

The substituted - 6,11 - dihydrodibenz-
[b,e]oxepine - 11 - ones used as starting
materials in this reaction are prepared by the
conventional methods of organic chemistry.
For instance, 2 - trifluoromethylthio - 6,11-
dihydrodibenz[b,e]oxepine - 11 - one is pre-
pared from the corresponding 2 - methylthio
compound (B. M. Bloom et al., Belgian Patent
No. 614,498, dated June 18, 1964) by first

chlorinating the side chain of the latter in the
presence of ultraviolet light to form the 2 - tri-
chloromethylthio derivative thereof, followed
by a subsequent heat treatment step with anti-
mony trifluoride at high temperatures to give
the desired fluoro analog. The 2 - trifluoro-
methylsulfinyl and 2 - trifluoromethylsulfonyl-
6,11 - dihydrodibenz[b,e]oxepine - 11 - ones
are then, respectively, each prepared from the
aforementioned 2 - trifluoromethylthio com-
pound by means of selective oxidative pro-
cedures well-known to those skilled in the art.

The phosphorane starting materials, on the
other hand, are generated into the reaction
mixture *in situ* from the corresponding phos-
phonium salt compounds in accordance with
the method of J. R. Tretter, as described in
Belgium Patent No. 654,283, dated April 12,
1965. This method generally involves the use
of at least two moles of a strong base such as
n - butyl lithium to convert the phosphonium
halide hydrohalide salt to the desired "ylide"
or phosphorane compound. Since the latter
product tends to be somewhat rather unstable
on standing, it is usually preferred, in practice,
to use it immediately in the next reaction step
without any prior isolation from solution by
merely adding the required tricyclic ketone
(i.e., 2 - substituted - 6,11 - dihydrodibenz-
[b,e]oxepine - 11 - one) thereto. The ultimate
starting materials required for this reaction,
viz., the above referred to phosphonium salts,
are also known and described as such in the
aforementioned patent to Tretter.

The acids which are used to prepare the
pharmaceutically-acceptable acid solution salts
of this invention are those which form non-
toxic acid addition salts containing pharma-
ceutically acceptable anions, such as the hydro-
chloride and maleate, when reacted with the
aforementioned aminopropylidene base com-
pounds. Preferred acids for use in this con-
nection include hydrochloric acid, hydro-
bromic acid, hydriodic acid, nitric acid, sul-
furic acid, phosphoric acid, acetic acid, lactic
acid, citric acid, tartaric acid, oxalic acid,
gluconic acid, saccharic acid, benzoic acid,
succinic acid, maleic acid, methane-sulfonic
acid, ethanesulfonic acid, benzenesulfonic acid,
p - toluene - sulfonic acid, picric acid,
amsnonic acid (4,4' - diaminostilbene - 2,2'-
disulfonic acid) and pamoic acid (1,1'-
methylene - bis - 2 - hydroxy - 3 - naphthoic
acid).

As previously indicated, the 2 - substituted-
11 - aminopropylidene - 6,11 - dihydrodibenz-
[b,e]oxepine compounds of this invention are
valuable as tranquilizing agents, particularly in
view of their potent CNS depressant action.
Hence, they are useful in the treatment of
mental anxiety, nervous tension and certain
related excited states as well, with the *cis*-
isomers being especially useful in this connec-
tion in view of their highly potent CNS
depressant action and lack of significant side

effects. For instance, the *cis*-isomer of 2 - trifluoromethylsulfonyl - 11 - (3 - N,N - dimethylaminopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine hydrochloride, a typical and preferred agent of the present invention, has been found to cause significantly potent CNS depressant effects in both hyperactive (amphetamine-induced) rats and dogs when administered by the oral route of administration, without causing any untoward side effects, such as impaired mental alertness, to occur even when so administered to them for a period of several days. Further, these herein described compounds can be administered as tranquilizing agents by either the oral or parenteral routes of administration. In general, they are ordinarily administered in dosages ranging from about 0.3 mg. to about 3.0 mg. per kg. of body weight per day, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen.

In connection with the use of the 2 - substituted - 11 - aminopropylidene - 6,11 - dihydrodibenz[b,e]oxepine compounds of this invention for the treatment of agitated subjects, it is to be noted that these compounds may be administered either alone or in combination with pharmaceutically acceptable carriers by either of the two routes previously indicated, and that such administration can be carried out in both single and multiple dosages. More particularly, the novel compounds of this invention can be administered in wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, aqueous suspension, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents. Moreover, such oral pharmaceutical formulations can be suitably sweetened and/or flavored by means of various agents of the type commonly employed for just such purposes. In general, the therapeutically useful compounds of this invention are present in such dosage forms at concentration levels ranging from about 0.5% to about 90% by weight of the total composition, i.e., in amounts which are sufficient to provide the desired unit dosage previously indicated.

For purpose of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and dicalcium phosphate may be employed along with various disintegrants such as starch and preferably potato or tapioca starch, alginic acid, and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very

useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection would also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspension and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, with emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof. For purposes of parenteral administration, solutions of these particular 2 - substituted-11 - aminopropylidene - 6,11 - dihydrodibenz[b,e]oxepines in sesame or peanut oil or in aqueous-propylene glycol or N,N - dimethylformamide may be employed, as well as sterile aqueous solutions of the corresponding water-soluble, non-toxic mineral and organic acid addition salts previously enumerated. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are readily obtainable by standard techniques well-known to those skilled in the art.

This invention is still further illustrated by the following examples, which are not to be construed in any way or manner as imposing limitations upon the scope thereof. Examples I or III describe the preparation of intermediate compounds.

EXAMPLE I

Ten grams (10 g.) of 2 - Methylthio - 6,11-dihydrodibenz[b,e]oxepine - 11 - one (prepared as described in Belgian Patent No. 641,498 for the corresponding 3 - methylthio isomer) dissolved in 80 ml. of dry chloroform was treated with chlorine gas, while cooled in an ice-bath and illustrated by means of a sun-lamp, until no further hydrogen chloride gas evolved from the resulting reaction mixture. The excess chlorine gas was then removed from the mixture by bubbling dry nitrogen gas through the solution, and the organic solvent was thereafter removed by means of evaporation *in vacuo* to afford a residual material that was subsequently allowed to crystallize from n-hexane solution to give 14 g. of 2 - trichloromethylthio - 6,11 - dihydrodibenz[b,e]oxepine - 11 - one, m.p. 98-99°C.

Ten grams (10 g.) of the above trichloro compound and 7.5 g. of sublimed antimony trifluoride were then ground together *via* a mortar and pestle, and the resulting mixture next heated in an oil bath at 240°C. while

under a nitrogen atmosphere. After five minutes of heating under these conditions, the flask was removed from the oil bath and the cooled residue was triturated with chloroform.

5 The combined chloroform extracts were then washed with water and subsequently evaporated to dryness while under reduced pressure to afford 11 g. of crude residual material that gave 2.3 g. of 2 - trifluoromethylthio - 6,11-dihydrodibenz[b,e]oxepine - 11 - one, m.p. 75—77°C., when chromatographed over an alumina column with benzene. Recrystallization of this material from methanol-water raised the final melting point to 79—82°C.

15 *Anal.* Calcd. for $C_{15}H_9F_3O_2S$: C, 58.05; H, 2.93; S, 10.33

Found: C, 58.46; H, 3.07; S, 10.84.

EXAMPLE II

20 A solution of 64.8 g. of p - trifluoromethylthiophenol in 640 ml. of xylene containing 21.9 g. of potassium hydroxide was refluxed for 1.5 hours while under a nitrogen atmosphere, during which time 10 ml. of water collected and the potassium salt of the resulting phenol precipitated from solution. Dry phthalide was then added to the system in one—44.5 g. portion, and the resulting mixture was thereafter refluxed for 21 hours. Upon cooling, 300 ml. of 10% aqueous potassium hydroxide were added and the spent reaction mixture was subsequently cooled in an icebath. The potassium salt which soon precipitated from solution was then collected by means of suction filtration and converted to the corresponding organic acid by means of suspension in 500 ml. of water, followed by acidification with 1N hydrochloric acid. The final precipitate which formed was then collected and washed with water to give 47.8 g. of product, viz., 2-(p - trifluoromethylthiophenoxymethyl)benzoic acid, m.p. 160—162°C.

Anal. Calcd. for $C_{15}H_{11}F_3O_3S$: C, 54.87; H, 3.38; S, 9.76.

Found: C, 54.64; H, 3.50; S, 9.39.

45 To a suspension of 153 g. of phosphorous pentoxide in 1300 ml. of benzene, there were added 47.8 g. of the above prepared acid (m.p. 160—162°C.), and the resulting mixture was thereafter stirred at reflux for a period of three hours while under a nitrogen atmosphere. At this point, the benzene was removed from the mixture by means of decanting and the residue was subsequently washed with 200 ml. portions of fresh benzene solvent. The combined benzene extracts were then next washed with water, dried over anhydrous magnesium sulfate and filtered. Evaporation of the dried filtrate, while under reduced pressure, then gave a residual oil which was subsequently triturated with n - hexane to afford 21 g. of 2 - trifluoromethylthio - 6,11 - dihydrodibenz[b,e]oxepine - 11 - one in the form of a crystalline precipitate, melting at 83—84°C.

EXAMPLE III

65 A solution consisting of 1.12 g. of 2 - trifluoromethylthio - 6,11 - dihydrodibenz[b,e]oxepine - 11 - one and 1.24 g. of m - chloroperbenzoic acid dissolved in 15 ml. of chloroform was refluxed for 1.5 hours. Upon cooling, a precipitate of m - chlorobenzoic acid soon formed and this material was subsequently isolated from the reaction mixture by means of suction filtration. The resulting filtrate was then evaporated to dryness under reduced pressure and the residue was chromatographed over silica gel to give two different polar fractions. The less polar fraction was 2 - trifluoromethylsulfonyl - 6,11 - dihydrodibenz[b,e]oxepine - 11 - one, m.p. 89—90°C. after crystallization from methanol-water. The more polar fraction, which followed later, proved to be 2 - trifluoromethylsulfinyl - 6,11 - dihydrodibenz[b,e]oxepine - 11 - one, m.p. 104—106°C. after crystallization from methanol-water.

EXAMPLE IV

90 A suspension of 3.09 g. (0.00605 mole) of anhydrous N,N - dimethylaminopropyltriphenylphosphonium bromide hydrobromide in 15 ml. of dry tetrahydrofuran was treated with two molecular equivalents of 1.64 M n-butyl lithium in n-hexane, while under a dry nitrogen atmosphere. After stirring the mixture for fifteen minutes at room temperature (25°C.), 1.5 g. of 2 - trifluoromethylthio - 6,11 - dihydrodibenz[b,e]oxepine - 11 - one were added and stirring was continued for an additional 1.5 hours thereafter. At the end of this time, 5 ml. of water were added to the spent reaction mixture and the organic solvents were subsequently removed therefrom by means of evaporation under reduced pressure. The residue was then distributed between benzene and dilute hydrochloric acid, and the benzene extracts were subsequently collected and thereafter partially evaporated to dryness and digested with n-hexane to afford the *cis*-isomer of 2 - trifluoromethylthio - 11 - (3-N,N - dimethylaminopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine hydrochloride in the form of a crystalline precipitate, m.p. 168—169°C.

Anal. Calcd. for $C_{20}H_{20}F_3NOS.HCl_{1/2}.H_2O$: C, 56.50; H, 5.22.

Found: C, 56.36; H, 5.16.

115 Crystallization of the residue obtained from the above mother liquor (of the *cis*-isomer), from ethyl acetate-hexane, then gave the corresponding *trans*-isomer of 2 - trifluoromethylthio - 11 - (N,N - dimethylaminopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine hydrochloride, m.p. 218—220°C.

Anal. Calcd. for $C_{20}H_{20}F_3NOS.HCl_{1/2}.H_2O$: C, 56.50; H, 5.22.

Found: C, 56.54; H, 5.16.

125 Subsequent conversion of each of the above hydrochlorides to the corresponding free or-

ganic base compound, in each case *via* treatment with 5N NaOH, then affords the pure 2 - trifluoromethylthio - 11 - (3 - N,N - dimethylaminopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine isomer.

EXAMPLE V

A suspension of 2.02 g. (0.00395 moles) of anhydrous N,N - dimethylaminopropyltriphenylphosphonium bromide in 10 ml. of dry tetrahydrofuran was treated with two molecular equivalents of 1.64 M n-butyl lithium in n-hexane, while under a dry nitrogen atmosphere. After stirring the mixture for fifteen minutes at room temperature ($\approx 25^\circ\text{C}$.), 1.08 g. of 2 - trifluoromethylsulfonyl - 6,11 - dihydrodibenz[b,e]oxepine - 11 - one were added and stirring was continued for an additional two hours. At the end of this time, 5 ml. of water were added to the spent reaction mixture and the organic solvents were subsequently removed therefrom by means of evaporation under reduced pressure. The residue was then distributed between benzene and dilute hydrochloric acid, and the acid extracts were thereafter combined, basified and extracted with fresh portions of benzene. The oily-residue obtained upon evaporation of the latter extracts to near dryness amounted to a *cis/trans* mixture of the desired final product, viz., 2 - trifluoromethylsulfonyl - 11 - (3 - N,N - dimethylaminopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine, which was subsequently converted to the hydrochloride salt and recrystallized from ethanol-diethyl ether to give the pure *cis*-isomer of 2 - trifluoromethylsulfonyl - 11 - (N,N - dimethylaminopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine hydrochloride, m.p. 219.5—220.5°C.

Anal. Calcd. for $\text{C}_{22}\text{H}_{22}\text{F}_3\text{N}_2\text{O}_3\text{S}\cdot\text{HCl}$: C, 53.63; H, 4.73.

Found: C, 53.38; H, 4.83.

Crystallization of the residue from the *cis*-isomer mother liquor obtained above, from ethyl acetate/n-hexane, then gave the corresponding *trans*-isomer of 2 - trifluoromethylsulfonyl - 11 - (N,N - dimethylaminopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine hydrochloride, m.p. 190—192°C.

Subsequent conversion of each of the above hydrochlorides to the corresponding free base compound, as in the preceding Example, then affords the pure 2 - trifluoromethylsulfonyl - 11 - (3 - N,N - dimethylaminopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine isomer as such.

EXAMPLE VI

A suspension of 3.91 g. (0.0079 mole) of anhydrous N - monomethylaminopropyltriphenylphosphonium bromide hydrobromide in 15 ml. of dry tetrahydrofuran was treated with two molecular equivalents of a n-hexane solution of n-butyl lithium while under a dry nitrogen atmosphere. After stirring the result-

ing mixture for fifteen minutes at room temperature ($\approx 25^\circ\text{C}$.), 2.0 g. of 2 - trifluoromethylthio - 6,11 - dihydrodibenz[b,e]oxepine - 11 - one were added thereto and stirring was continued for an additional 16 hours. At the end of this time, 5 ml. of water were added to the spent reaction mixture and the organic solvents were subsequently removed therefrom by means of evaporation under reduced pressure. The residue was then partitioned between benzene and dilute hydrochloric acid, and the removed benzene layer was thereafter partially evaporated to dryness and digested with n-hexane, followed by subsequent treatment with ethanol - diethyl ether to give the *cis*-isomer of 2 - trifluoromethylthio - 11 - (3 - N - monomethylaminopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine hydrochloride, m.p. 190—191.5°C.

Anal. Calcd. for $\text{C}_{19}\text{H}_{18}\text{F}_3\text{NOS}\cdot\text{HCl}$: C, 56.78; H, 4.76.

Found: C, 57.00; H, 4.79.

The corresponding *trans*-isomer of 2 - trifluoromethylthio - 11 - (3 - N - monomethylaminopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine hydrochloride was then isolated from *cis*-isomer mother liquor obtained above and crystallized from ethyl acetate to form an analytically pure sample, m.p. 236—237°C.

Anal. Calcd. for $\text{C}_{19}\text{H}_{18}\text{F}_3\text{NOS}\cdot\text{HCl}$: C, 56.78; H, 4.76.

Found: C, 46.50; H, 4.79.

Subsequent conversion of each of the above hydrochlorides to the free base compound in each case (*via* 5N NaOH) then affords the corresponding 2 - trifluoromethylthio - 11 - (3 - N - monomethylaminopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine base isomer in pure form as such.

EXAMPLE VII

A suspension of 11.0 g. of anhydrous N - monomethylaminopropyltriphenylphosphonium bromide hydrobromide in 45 ml. of dry tetrahydrofuran was treated with two molecular equivalents of n-butyl lithium in n-hexane, while under a dry nitrogen atmosphere. After stirring the resulting mixture for fifteen minutes at room temperature ($\approx 25^\circ\text{C}$.), the ylide solution was cooled to 0°C . and 6.1 g. of 2 - trifluoromethylsulfonyl - 6,11 - dihydrodibenz[b,e]oxepine - 11 - one added with continued stirring at this point for an additional two hours. Stirring was then maintained for an additional two hours thereafter, while heating the system at reflux temperatures. At the end of this time, 25 ml. of water were added to the cooled reaction mixture and the organic solvents present were subsequently removed therefrom by means of evaporation under reduced pressure. The residue was then distributed between benzene and dilute hydrochloric acid, and the collected benzene extracts were thereafter washed with

dilute aqueous sodium hydroxide solution and water, followed by a careful treatment with *N* sulfuric acid in a dropwise manner accompanied by vigorous stirring. In this manner, there was soon obtained a crystalline precipitate of the desired *cis*-isomer of 2 - trifluoromethylsulfonyl - 11 - (3 - *N* - monomethylaminopropylidene) - 6,11 - dihydrodibenz[*b,e*]oxepine hydrogen sulfate, m.p. 236.5—237°C.

Anal. Calcd. for $C_{17}H_{18}F_3NO_3S \cdot 1/2H_2O$: C, 50.20; H, 4.40; N, 3.08; S, 10.58.

Found: C, 50.28; H, 4.47; N, 3.03; S, 10.68.

Subsequent conversion of the above hydrogen sulfate salt to the corresponding free base compound as in the preceding Example, then affords the pure base isomer as such, viz., *cis*-2 - trifluoromethylsulfonyl - 11 - (3 - *N*-monomethylaminopropylidene) - 6,11 - dihydrodibenz[*b,e*]oxepine.

EXAMPLE VIII

A suspension of 28.0 g. (0.051 mole) of anhydrous *N* - piperazinopropyltriphenylphosphonium bromide hydrobromide in 140 ml. of dry tetrahydrofuran was treated with 70 ml. of 1.63 *M* *n*-butyl lithium in *n*-hexane, while under a dry nitrogen atmosphere. The rate of addition of the organo-metallic reagent to the organic suspension was such that the temperature of the mixture remained just below the reflux point. After stirring the resulting mixture for fifteen minutes, the ylide solution was placed in a syringe and added therefrom into a solution consisting of 14.0 g. (0.041 mole) of 2 - trifluoromethylsulfonyl - 6,11 - dihydrodibenz[*b,e*]oxepine - 11 - one dissolved in 70 ml. of tetrahydrofuran that had already been stirred at reflux. After the addition was complete (this required about 10—20 minutes), refluxing was continued for a further two hours and the reaction mixture was then cooled to room temperature (25°C.). At the end of this time, 50 ml. of water were added to the mixture and the organic solvents present in the system were subsequently evaporated therefrom while *in vacuo*. The residue was then treated with 200 ml. of benzene, followed by *N* hydrochloric acid solution until the pH of the resulting aqueous phase was in the range of pH 1—3. The benzene layer was then removed and washed with four-25 ml. portions of *N* hydrochloric acid, and the combined acid extracts were thereafter adjusted to pH 11 with 10% aqueous sodium hydroxide and re-extracted with four-50 ml. portions of fresh benzene. The latter benzene extracts were then washed

with water, dried with anhydrous sodium sulfate and filtered. Upon subsequent evaporation of the resulting filtrate, there was obtained a 55% yield of crude organic base material as the residue.

The above crude base compound, which is 2 - trifluoromethylsulfonyl - 11 - (3 - *N*-piperazinopropylidene) - 6,11 - dihydrodibenz[*b,e*]oxepine, was then dissolved in ethanol (10 g./50 ml.) and treated with a small amount of activated charcoal, while being warmed. After removal of the carbon particles by means of filtration, solid maleic acid was added to the resulting alcoholic solution in small portions, with stirring, until the pH became pH 2—3, followed by the addition of seed crystals of the product. Stirring was then continued at room temperature until crystallization was complete and the mixture thereafter cooled in an ice-bath before filtration was carried out. After collecting the solid crystalline particles on a filter funnel in this manner, and thereafter washing same with small fresh portions of ethanol and ether, there was obtained a pure crystalline material which after one recrystallization from ethanol gave the pure *cis*-isomer of 2 - trifluoromethylsulfonyl - 11 - (3 - *N* - piperazinopropylidene) - 6,11 - dihydrodibenz[*b,e*]oxepine dimaleate, m.p. 170—171°C.

Anal. Calcd. for $C_{22}H_{22}F_3N_2O_3S \cdot 2C_4H_4O_4$: C, 52.62; H, 4.56.

Found: C, 52.79; H, 4.78.

Subsequent conversion of each of the above maleate salts to the corresponding free base compound, in each case *via* 5*N* NaOH, then affords the pure 2 - trifluoromethylsulfonyl - 11 - (3 - *N* - piperazinopropylidene) - 6,11 - dihydrodibenz[*b,e*]oxepine isomer as such (the picrate of the *cis*-isomer melted at 234—236°C.).

EXAMPLE IX

The procedure described in the preceding Examples is employed here to prepare the following aminopropylidene base compounds starting from the appropriate 2 - substituted-6,11 - dihydrodibenz[*b,e*]oxepine - 11 - one and 3 - aminopropyltriphenylphosphonium bromide hydrobromide reagent in each case:



| Y | Z | Y | Z |
|---------------|-------------------------------------|---------------|---|
| S | $-\text{NHC}_2\text{H}_5$ | SO_2 | $-\text{N}(\text{n}-\text{C}_4\text{H}_9)_2$ |
| SO | $-\text{HNCH}_3$ | S | $-\text{N} \begin{array}{c} \text{---} \text{---} \text{---} \text{---} \end{array} (\text{CH}_2)_4$ |
| SO_2 | $-\text{NHC}_2\text{H}_5$ | SO | $-\text{N}(\text{i}-\text{C}_3\text{H}_7)_2$ |
| S | $-\text{NHC}_3\text{H}_7(\text{i})$ | SO_2 | $-\text{N} \begin{array}{c} \text{---} \text{---} \text{---} \text{---} \end{array} (\text{CH}_2)_4$ |
| SO | $-\text{NHC}_2\text{H}_5$ | S | $-\text{N} \begin{array}{c} \text{---} \text{---} \text{---} \text{---} \end{array} (\text{CH}_2)_5$ |
| SO_2 | $-\text{NHC}_3\text{H}_7(\text{i})$ | SO | $-\text{N}(\text{n}-\text{C}_4\text{H}_9)_2$ |
| S | $-\text{NHC}_4\text{H}_9(\text{n})$ | SO_2 | $-\text{N} \begin{array}{c} \text{---} \text{---} \text{---} \text{---} \end{array} (\text{CH}_2)_5$ |
| SO | $-\text{NHC}_3\text{H}_7(\text{i})$ | S | $-\text{N} \begin{array}{c} \text{---} \text{---} \text{---} \text{---} \end{array} (\text{CH}_2)_6$ |
| SO_2 | $-\text{NHC}_4\text{H}_9(\text{n})$ | SO | $-\text{N} \begin{array}{c} \text{---} \text{---} \text{---} \text{---} \end{array} (\text{CH}_2)_4$ |
| S | $-\text{N}(\text{C}_2\text{H}_5)_2$ | SO_2 | $-\text{N} \begin{array}{c} \text{---} \text{---} \text{---} \text{---} \end{array} (\text{CH}_2)_6$ |
| SO | $-\text{NHC}_4\text{H}_9(\text{n})$ | S | $-\text{N} \begin{array}{c} \text{---} \text{---} \text{---} \text{---} \end{array} (\text{CH}_2)_2 \text{O} (\text{CH}_2)_2$ |
| SO_2 | $-\text{N}(\text{C}_2\text{H}_5)_2$ | SO | $-\text{N} \begin{array}{c} \text{---} \text{---} \text{---} \text{---} \end{array} (\text{CH}_2)_5$ |

| Y | Z | Y | Z |
|---------------|--|---------------|--|
| S | $-\text{N}(\text{i}-\text{C}_3\text{H}_7)_2$ | SO_2 | $-\text{N}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$ |
| SO | $-\text{N}(\text{CH}_3)_2$ | S | $-\text{N}(\text{CH}_2)_2\text{S}(\text{CH}_2)_2$ |
| SO_2 | $-\text{N}(\text{i}-\text{C}_4\text{H}_9)_2$ | SO | $-\text{N}(\text{CH}_2)_6$ |
| S | $-\text{N}(\text{n}-\text{C}_4\text{H}_9)_2$ | SO_2 | $-\text{N}(\text{CH}_2)_2\text{S}(\text{CH}_2)_2$ |
| SO | $-\text{N}(\text{C}_2\text{H}_5)_2$ | S | $-\text{N}(\text{CH}_2)_2\text{NH}(\text{CH}_2)_2$ |
| SO | $-\text{N}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$ | SO_2 | $-\text{N}(\text{CH}_2)_2\text{NH}(\text{CH}_2)_2$ |
| S | $-\text{N}(\text{CH}_2)_2\text{N}(\text{CH}_3)(\text{CH}_2)_2$ | SO | $-\text{N}(\text{CH}_2)_2\text{S}(\text{CH}_2)_2$ |
| SO_2 | $-\text{N}(\text{CH}_2)_2\text{N}(\text{CH}_3)(\text{CH}_2)_2$ | S | $-\text{N}(\text{CH}_2)_2\text{N}(\text{C}_2\text{H}_5)(\text{CH}_2)_2$ |
| SO | $-\text{N}(\text{CH}_2)_2\text{NH}(\text{CH}_2)_2$ | SO_2 | $-\text{N}(\text{CH}_2)_2\text{N}(\text{C}_2\text{H}_5)(\text{CH}_2)_2$ |
| S | $-\text{N}(\text{CH}_2)_2\text{N}(\text{i}-\text{C}_3\text{H}_7)(\text{CH}_2)_2$ | SO | $-\text{N}(\text{CH}_2)_2\text{N}(\text{CH}_3)(\text{CH}_2)_2$ |
| SO_2 | $-\text{N}(\text{CH}_2)_2\text{N}(\text{i}-\text{C}_3\text{H}_7)(\text{CH}_2)_2$ | S | $-\text{N}(\text{CH}_2)_2\text{N}(\text{n}-\text{C}_4\text{H}_9)(\text{CH}_2)_2$ |
| SO | $-\text{N}(\text{CH}_2)_2\text{N}(\text{n}-\text{C}_4\text{H}_9)(\text{CH}_2)_2$ | SO_2 | $-\text{N}(\text{CH}_2)_2\text{N}(\text{n}-\text{C}_4\text{H}_9)(\text{CH}_2)_2$ |

EXAMPLE X

A solution consisting of 3.5 g. of 2 - trifluoromethylsulfonyl - 11 - (3 - N - piperazinopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine (as free base compound) dissolved in 31 ml. of 97% formic acid and containing 35 ml. of 37% aqueous formaldehyde was warmed gently by heating on a steam bath for 1.5 hours. At the end of this time, 100 ml. of water were added and the resulting mixture was treated with 10% aqueous sodium hydroxide solution until the pH became pH 10—11. Extractions of the thus obtained

aqueous solution with diethyl ether, followed by evaporation of the latter solvent from the ethereal extracts then afforded the desired product, i.e., 2 - trifluoromethylsulfonyl - 11 - [3 - (4 - methyl - 1 - piperazinyl) - propylidene] - 6,11 - dihydrodibenz[b,e]oxepine, in the form of its crude base. The hydrochloride salt was subsequently prepared therefrom using an ethanol-diethyl ether medium to give the pure *cis*-isomer of 2 - trifluoromethylsulfonyl - 11 - [3 - (4 - methyl - 1 - piperazinyl) - propylidene] - 6,11 - dihydrodibenz[b,e]oxepine hydrochloride, m.p. 234—235°C.

Anal. Calcd. for $C_{27}H_{25}F_3N_2O_3S \cdot 2HCl \cdot \frac{1}{2}H_2O$: C, 50.18; H, 5.10; N, 5.11; F, 10.37.
Found: C, 49.80; H, 5.36; N, 5.01; F, 10.36.

Subsequent conversion of the above hydrochloride to the corresponding free compound *via* 5N NaOH then affords the pure isomer as such, viz., *cis* - 2 - trifluoromethylsulfonyl - 11 - [3 - (4 - methyl - 1 - piperazinyl)propylidene] - 6,11 - dihydrodibenz[b,e]oxepine.

dibenz[b,e]oxepine as the final product which is obtained.

EXAMPLE XII

The procedure described in the previous Example is repeated using 2 - trifluoromethylthio - 11 - (3 - N - piperazinopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine as starting material in place of the corresponding 2 - trifluoromethylsulfonyl compound. In this particular case, the final product obtained is 2 - trifluoromethylthio - 11 - [3 - (4 - methyl - 1 - piperazinyl)propylidene] - 6,11 - dihydrodibenz[b,e] - oxepine. In like manner, 2 - trifluoromethylsulfinyl - 11 - (3 - N - piperazinopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine and 37% aqueous formaldehyde in 97% formic acid react to afford 2 - trifluoromethylsulfinyl - 11 - [3 - (4 - methyl - 1 - piperazinyl) - propylidene] - 6,11 - dihydro-

A solution consisting of 3.0 g. of 2 - trifluoromethylsulfonyl - 11 - (3 - N - piperazinopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine (as the free base compound) dissolved in 75 ml. of dry methanol was treated with 750 mg. of ethylene oxide gas and the resulting mixture refluxed gently for two hours. At the end of this time, the solvent was removed by means of evaporation under reduced pressure and the residual material, i.e., the crude base consisting of 2 - trifluoromethylsulfonyl - 11 - [3 - (4 - β - hydroxyethyl - 1 - piperazinyl)propylidene] - 6,11 - dihydrodibenz[b,e] - oxepine, was thereafter converted to the hydrochloride salt to afford the pure *cis*-isomer of 2 - trifluoromethylsulfonyl - 11 - [3 - (4 - β - hydroxyethyl - 1 - piperazinyl)propylidene] - 6,11 - dihydrodibenz[b,e]oxepine hydrochloride, m.p. 234—235°C. after one recrystallization from isopropanol - diethyl ether.

Anal. Calcd. for $C_{27}H_{27}F_3N_2O_3S \cdot 2HCl$: C, 50.62; H, 5.13; Cl, 12.45.
Found: C, 50.64; H, 5.55; Cl, 12.54.

Subsequent conversion of the above hydrochloride to the corresponding free base compound as in Example X, then affords pure *cis* - 2 - trifluoromethylsulfonyl - 11 - [3 - (4 - β - hydroxyethyl - 1 - piperazinyl)propylidene] - 6,11 - dihydrodibenz[b,e] - oxepine isomer as the product which is obtained.

sulfonyl - 11 - (3 - N - piperazinopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine and 1,2 - butylene oxide react to afford 2 - trifluoromethylsulfonyl - 11 - [3 - (4 - β - hydroxybutyl - 1 - piperazinyl)propylidene] - 6,11 - dihydrodibenz[b,e]oxepine, while 2,3-butylene oxide in the same reaction gives 2 - trifluoromethylsulfonyl - 11 - (3 - [4 - (α - methyl - β hydroxypropyl) - 1 - piperazinyl] - propylidene) - 6,11 - dihydrodibenz[b,e]oxepine.

EXAMPLE XIII

The procedure described in the preceding Example is repeated here except that 1,2-propylene oxide is the reagent employed instead of ethylene oxide and 2 - trifluoromethylsulfonyl - 11 - [3 - (4 - β hydroxypropyl - 1 - piperazinyl)propylidene] - 6,11 - dihydrodibenz[b,e]oxepine is the corresponding product obtained. In like manner, 2 - trifluoromethyl-

When 2 - trifluoromethylthio - 11 - (3 - N - piperazinopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine and 2 - trifluoromethylsulfinyl - 11 - (3 - N - piperazinopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine are each respectively employed as starting materials in this

series of oxyalkylation reactions, the following compounds are the final products actually obtained:

- 2 - trifluoromethylthio - 11 - {3 - (4 - β -hydroxyethyl - 1 - piperazinyl)propylidene} - 6,11 - dihydrodibenz[b,e]oxepine.
 2 - trifluoromethylsulfinyl - 11 - {3 - (4 - β - hydroxyethyl - 1 - piperazinyl)propylidene} - 6,11 - dihydrodibenz[b,e]oxepine.
 2 - trifluoromethylthio - 11 - {3 - (4 - β -hydroxypropyl - 1 - piperazinyl)propylidene} - 6,11 - dihydrodibenz[b,e]oxepine
 2 - trifluoromethylsulfinyl - 11 - {3 - (4 - β - hydroxypropyl - piperazinyl)propylidene} - 6,11 - dihydrodibenz[b,e]oxepine
 2 - trifluoromethylthio - 11 - {3 - (4 - β -hydroxybutyl - 1 - piperazinyl)propylidene} - 6,11 - dihydrodibenz[b,e]oxepine
 2 - trifluoromethylsulfinyl - 11 - {3 - (4 - β - hydroxybutyl - 1 - piperazinyl)propylidene} - 6,11 - dihydrodibenz[b,e]oxepine
 2 - trifluoromethylthio - 11 - {3 - (4 - (α -methyl - β - hydroxypropyl) - 1 - piperazinyl)propylidene} - 6,11 - dihydrodibenz[b,e]oxepine
 2 - trifluoromethylsulfinyl - {3 - (4 - (α -methyl - β - hydroxypropyl) - 1 - piperazinyl)propylidene} - 6,11 - dihydrodibenz[b,e]oxepine

EXAMPLE XIV

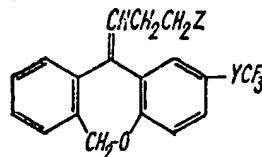
The hydrochloric acid addition salts of the novel aminopropylidene base compounds of this invention are prepared by dissolving the free organic base compound in an aqueous acetone solution containing an equivalent amount in moles of N hydrochloric acid. Upon careful evaporation of the resultant solution to dryness while under reduced pressure, there is obtained the desired hydrohalide acid addition salt in the form of a crystalline residue. In this manner, 2 - trifluoromethylsulfinyl - 11 - (3 - N,N - dimethylaminopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine and hydrochloric acid react to afford 2 - trifluoromethylsulfinyl - 11 - (3 - N,N - dimethylaminopropylidene) - 6,11 - dihydrodibenz[b,e]oxepine hydrochloride.

In like manner, other acid addition salts of the aminopropylidene base compounds reported previously in the preceding Examples are prepared here by using the said organic base compounds as starting materials in every instance and hydrochloric, hydrobromic, hydriodic, nitric, sulfuric, phosphoric, acetic, lactic, maleic, citric, tartaric, oxalic, gluconic,

saccharic, benzoic, succinic, methanesulfonic, ethanesulfonic, benzenesulfonic, p - toluenesulfonic, amsonic, pamoic and picric acids, as the respective reagents in each and every case.

WHAT WE CLAIM IS:—

1. Aminopropylidene bases of the formula:



and the pharmaceutically-acceptable acid addition salts thereof, wherein Y is sulfur, sulfinyl or sulfonyl; and Z is lower alkylamino, di-(lower alkyl)amino, pyrrolidino, piperidino, homopiperidino, morpholino, thiamorpholino, piperazino, N - (lower alkyl)piperazino or N-(lower hydroxyalkyl)piperazino, wherein said lower alkyl moieties contain up to four carbon atoms.

2. A compound as claimed in Claim 1 wherein Y is sulfonyl and Z is dimethylamino.

3. A compound as claimed in Claim 1 wherein Y is sulfonyl and Z is N - methylpiperazino.

4. A compound as claimed in Claim 1 wherein Y is sulfonyl and Z is N - (β -hydroxyethyl)piperazino.

5. A compound as claimed in Claim 1 wherein Y is sulfinyl and Z is dimethylamino.

6. A compound as claimed in Claim 1 wherein Y is sulfonyl and Z is monomethylamino.

7. A compound as claimed in Claim 1 wherein Y is sulfonyl and Z is piperazino.

8. A compound as claimed in Claim 1 wherein Y is sulfur and Z is monomethylamino.

9. A compound as claimed in Claim 1 wherein Y is sulfinyl and Z is N - methylpiperazino.

10. The *cis*-isomer of the compound as claimed in Claim 2.

11. The *cis*-isomer of the compound as claimed in Claim 4.

12. The *cis*-isomer of the compound as claimed in Claim 8.

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